CARTICEL™

AUTOLOGOUS CULTURED CHONDROCYTES

for Implantation

DESCRIPTION

Autologous cultured chondrocytes, the Carticel™ product, are derived from *in vitro* expansion of autologous chondrocytes harvested from a patient's normal, femoral articular cartilage. Biopsies from a lesser-weight bearing area are the source of chondrocytes which are isolated, expanded through cell culture, and ultimately implanted into articular cartilage defects beneath an autologous periosteal flap. Each single use container of autologous cultured chondrocytes has approximately 12 million cells aseptically processed and suspended in 0.4 mL of sterile, buffered Dulbecco's Modified Eagles Medium (DMEM). Prior to final packaging, cell viability is assessed to be at least 80%.

CLINICAL PHARMACOLOGY

Studies have shown that implantation of the Carticel™ product into the articular defect can result in the development of hyaline cartilage (see Clinical Experience). Hyaline cartilage consists of chondrocytes (≤ 5% total volume) and extracellular matrix (≥ 95% total volume). The matrix contains a variety of macromolecules, including type II collagen and proteoglycan. The structure of the matrix allows the cartilage to absorb shock and withstand shearing and compression forces. Normal hyaline cartilage also has an extremely low coefficient of friction at the articular surface. Damage to articular cartilage from acute or repetitive trauma often results in pain and disability. Partly because hyaline cartilage is avascular, spontaneous healing of large defects is not believed to occur in humans, though a variety of surgical procedures have been used in attempts to promote repair of cartilage. As cartilage heals after these procedures, fibrocartilage rather than hyaline cartilage is most commonly produced. Fibrocartilage has limited ability to withstand shock and shearing forces.

Clinical Experience: Clinical information regarding the use of autologous cultured chondrocytes is available from 2 sources:
1) a series of patients treated in Sweden, and 2) a U.S. patient registry. Patients in the Swedish series received an autologous cultured chondrocyte product which was produced slightly differently than Carticel™, the U.S. product.

The series consists of 153 consecutive patients who received autologous cultured chondrocyte implantations for various defects of the knee. Clinical follow-up ranged from 1 week to 94 months. Most patients had arthroscopic evaluation; a subset had biopsy and histological evaluations. Patients presented with cartilaginous defects of the femoral condyle, patella, tibia, a combination of these, or osteochondritis dissecans, with or without non-cartilaginous defects such as anterior cruciate ligament damage requiring repair.

Following autologous cultured chondrocyte implantation, patients were routinely followed for various durations. All patients were retrospectively classified as having one of the three clinical outcomes: resumed all activities, some improvement, or no improvement. Clinical outcomes were also reported for patient subgroups including: 1) those with femoral condyle lesions who had at least 18 months of follow-up, and 2) those who failed an earlier procedure. Most patients were also assessed for arthroscopic outcomes and some patients were assessed for histological outcomes.

Clinical Outcome - Patients with Femoral Condyle Lesions
A total of 78 of 153 patients in the Swedish series had femoral condyle lesions with or without concurrent non-cartilaginous knee lesions. Patients had one or more defects ranging in size from <1-20 cm^2. Approximately 90% of the patients had defects of <10 cm^2. Clinical outcomes are shown below for 40 patients who received autologous cultured chondrocytes and were evaluable after at least 18 months of follow-up (median = 25; range = 18-94 months). In this evaluation, 28% (11/40) of the patients had "resumed all activities" and 42% (17/40) of the patients had demonstrated "some improvement," for a total of 70% demonstrating some clinical benefit when compared to their pre-operative condition.

Patient Response to Treatment

	Resumed all activities	Some improvement	No improvement	Total
Defect				
Femoral Condyle	7 (29%)	8 (33%)	9 (38%)	24
Femoral Condyle plus Other Non-Cartilage Repair	4 (25%)	9 (56%)	3 (19%)	16
Total	11 (28%)	17 (42%)	12 (30%)	40

No apparent association of clinical outcomes with lesion size or cell dose could be demonstrated.

Clinical Outcome - Failed Earlier Procedures
Debridement of the cartilage defect is often performed along with Carticel™ administration. To help differentiate the effects of the autologous cultured chondrocyte implantation procedure from those of debridement alone, an analysis was performed on 22 patients who had failed prior debridement and had a follow-up period after autologous cultured chondrocyte implantation which was greater than the time period to failure of their initial debridement. These patients had a range of cartilage defects. At the end of follow-up, 5 (23%) patients had a functional outcome rating of "resumed all activities," 8 (36%) patients had a rating of "some improvement," and 9 (41%) patients had a rating of "no improvement." Thus, 13/22 (59%) patients who had failed an earlier debridement had outcomes following autologous cultured chondrocyte implantation which were more favorable and durable than those following their earlier therapy.

Histological Outcome
Twenty-two of the initial 23 patients in the Swedish series had histological evaluation of biopsies from the transplant site. Fifteen of those patients had defects of the femoral condyle and 7 had defects of the patella. Six of the 15 femoral condyle patients showed only hyaline cartilage on their biopsy, 5 had a mixture of hyaline and fibrocartilage, and 4 had only fibro-cartilage. Of the 6 patients with only hyaline cartilage on biopsy, 2 had minimal to no defects and 4 had more extensive defects (e.g., fissures, fibrillations, etc.).

Arthroscopic Outcome
Most of the 153 patients had arthroscopy. The quality of repair observed at arthroscopy correlated with the clinical outcomes. A substantial number of patients were noted at arthroscopy to have tissue hypertrophy (see Adverse Events).

Data from the US registry included 38 patients with femoral condyle lesions who received the Carticel™ product and had at least 12 months of follow-up. Only functional outcome data were collected; no arthroscopic or histologic data are available. Although these patients were rated according to outcome measurements different from those used in the Swedish series, the results were consistent with the Swedish experience.

Two randomized, controlled post-marketing studies are under way to evaluate both long term functional outcomes, and the contribution of the cellular product to functional outcomes.

INDICATIONS AND USAGE

Carticel™ is indicated for the repair of clinically significant, symptomatic, cartilaginous defects of the femoral condyle (medial, lateral or trochlear) caused by acute or repetitive trauma.

Carticel™ is not indicated for the treatment of cartilage damage associated with osteoarthritis.

Carticel™ should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Data regarding functional outcomes beyond 3 years of autologous cultured chondrocyte treatment are limited.

WARNINGS

This tissue is intended for autologous use and has not been tested for biohazards. Health providers should handle this product as if infectious agents are present.

Carticel™ should not be used in patients with a known history of anaphylaxis to gentamicin. The biopsy medium used to transport the cartilage biopsies and the culture medium used during the first passage of cells contains DMEM with gentamicin. All subsequent processing is conducted aseptically and utilizes cell culture medium that does not contain gentamicin; however, trace quantities of gentamicin may still be present.

Carticel™ should not be used in patients with known sensitivities to materials of bovine origin. The cell culture medium used during the culturing of the cells contains bovine serum. The medium used to package and transport the cells does not contain serum; however, trace quantities of bovine-derived proteins may still be present.

PRECAUTIONS

General
Implantation of the Carticel™ product should be restricted to physicians who have completed Genzyme Tissue Repair's Surgeon Training Program.

Instability of the knee or abnormal weight-distribution within the joint may adversely affect the success of the procedure and should be corrected prior to Carticel™ implantation. Abnormal varus loading of the medial compartment may jeopardize the implant. When treating trochlear defects, abnormal patellar tracking must be corrected, if possible.

Physical activity should be resumed according to the rehabilitation plan recommended by the physician. Vigorous activity may compromise the durability of clinical benefit from Carticel™. Tissue hypertrophy was an observed adverse event in clinical studies (see Adverse Reactions). Patients who develop clinical signs of tissue hypertrophy should be evaluated with arthroscopy.

Both the long-term effect of cartilage harvesting on knee function and the long term safety of cartilage implantation are unknown.

The safety of the Carticel™ product is unknown in patients with malignancy in the area of cartilage biopsy or implant. The potential exists for *in vitro* expansion and subsequent implantation of malignant or dysplastic cells present in biopsy tissue. In addition, implantation of normal autologous chondrocytes could potentially stimulate growth of malignant cells in the area of the implant, although there have been no reported incidents in humans.

The Carticel™ product is shipped following a preliminary sterility test with a 48 hour incubation to determine absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of implantation.

Do Not Refrigerate, Freeze, or Incubate the Carticel™ Shipping Container or its Contents. The Carticel™ product consists of viable, autologous cells packaged and labeled for implantation within specified time limits. The Carticel™ transport box should be held at room temperature and remain closed until the time of implantation to ensure proper storage conditions for the cells.

Do Not Sterilize. If the Vial is Damaged or Sterility has been Compromised, Do Not Use.

Information for Patients

Patients receiving autologous cultured chondrocytes for treatment of an articular cartilage defect should receive the following information and instructions.
The rehabilitation protocol provided by the physician must be closely adhered to. Early motion is very important and should start with leg supported exercises gradually increasing the number of repetitions. If pain starts to develop as the next level of activity is increased, decrease activity to the former level until the pain resolves. If exercise causes pain and/or swelling, reduce the amount of physical activity. Swelling should be controlled using ice packs. When walking for the first 6 to 7 weeks, the treated knee should be supported with two crutches. The patient should attempt to walk with a normal gait, allowing a quarter of the body weight on the treated knee for the first 3 weeks, then gradually increasing the amount of weight. At anytime during the rehabilitation process or after, if sharp pain is experienced with locking or swelling, contact the physician for medical advice.

Pediatric Use

Safety and effectiveness of Carticel™ in pediatric populations has not been established.

ADVERSE EVENTS

General Adverse Events
Any intra-operative and post-operative complication following knee arthrotomy may occur after autologous cultured chondrocyte implantation. Of 153 patients treated with autologous cultured chondrocyte implantation in Sweden, 34 (22%) patients had the following adverse events (other than hypertrophic tissue, see below): intra-articular adhesions, 8%; superficial wound infection, 3%; hypertrophic synovitis, 3%; post-operative hematoma, 2%; adhesions of the bursa suprapatellaris, 2%; and hypertrophic synovium, 1%. About 1% of patients developed severe adhesions resulting in "frozen knee" and requiring lysis. Adverse reactions noted at a level of less than 1% included keloid-like scar, pannus formation, significant swelling of the joint, pain with post-operative fever, and hematoma following arthroscopy.

Tissue Hypertrophy
Of 86 patients with a range of defects and at least 18 months of follow-up, 37 (43%) had hypertrophic tissue noted at follow-up arthroscopy. In those clinically evaluable patients with femoral condyle defects, 10 of 40 (25%) had some hypertrophic tissue noted at follow-up arthroscopy. The hypertrophic tissue ranged from a small amount of diffuse excess tissue at the implantation site, to a distinct ridge of tissue at the margin of the implant, to widespread excess tissue throughout the joint space. Some of these patients had clinical symptoms including painful crepitations or "catching." Symptoms generally resolved after arthroscopic resection of the hypertrophic tissue. Ten percent of patients with hypertrophy required additional treatment after hypertrophic tissue recurred following initial resection.

In the U.S. registry, 44/241 patients had at least 12 months of follow-up and experienced similar types of adverse events as the patients in the Swedish series.

DOSAGE AND ADMINISTRATION

Patients in the Swedish series received a wide range of cell doses per cm^2 of defect. Available data on 70 of 78 patients with femoral condyle defects showed a median dose of 1.6 million cells/cm^2 of defect. The middle 80% of these patients received from 0.64 million to 3.3 million cells/cm^2. Each Carticel™ finished product vial contains approximately 12 million cells.

Implantation of the Carticel™ product is performed during arthrotomy and requires both preparation of the defect bed and a periosteal flap to secure the implant. Complete hemostasis must be achieved prior to periosteal fixation and cell implantation. See the Carticel™ Surgical Manual, GTR document #65021 for instructions on performance of these procedures.

Cell Aspiration and Implantation
(For complete surgical instructions, see Surgical Manual #65021.)
NOTE:
The exterior of the Carticel™ vial containing the cultured cells is NOT sterile. Follow strict sterile technique protocols.

When treating a defect which requires multiple vials of cells, resuspend, aspirate and inject one vial at a time.

1. Remove red plastic lid from vial. Wipe the vial surface and lid with alcohol.

2. Inspect vial contents for particulates, discoloration or turbidity. The cellular product appears as a yellowish clump in the bottom of the vial. Do not administer if contents appear turbid prior to cell suspension.

3. While holding vial in a vertical position, insert the needle of the intraspinal catheter into the vial. The needle must be positioned just above the fluid level. Slowly remove the inner needle from the catheter, leaving flexible tip behind. Attach a tuberculin syringe to catheter.

4. Lower the catheter tip into the media and position just above the cell pellet. Aspirate all the medium from the vial leaving only the cell pellet behind. Slowly expel medium back into the vial. This action will break the cell pellet and resuspend the cells in the medium.

5. Lower the catheter tip to the base of the vial and aspirate all contents into syringe, leaving the vial empty. Slowly inject the contents into the vial again. This will assure complete suspension of the cells. Repeat these steps as needed to ensure all cells are resuspended. Cell resuspension is complete when cell particles are no longer apparent, and the medium is a consistent, "cloudy" mixture. Aspirate all contents of vial into syringe. Always hold syringe vertical to keep an air pocket at the proximal end of syringe.

6. Insert the catheter tip through the superior opening of the periosteal chamber at the site the defect. Advance catheter to most inferior aspect of the defect.

7. Slowly inject a cell dose while moving the catheter tip from side to side and withdrawing the catheter proximally. This will ensure an even distribution of the cells throughout the defect.

8. Complete the implantation by closing the superior opening of the periosteum as instructed. See Carticel™ Surgical Manual.

HOW SUPPLIED

Each vial contains approximately 12 million autologous cells for a single implantation procedure. The vial of cells is placed within secondary packaging capable of maintaining the appropriate storage temperature and cell viability for up to 72 hours. The shipping vials containing chondrocytes are accompanied by a technical data sheet with detailed specifications for the processed cells. Maintain shipping carton at room temperature.

CAUTION

Federal Law restricts Carticel™ to sale and use by or on the order of a physician.
For more information or to obtain Genzyme Tissue Repair documents or references, contact:

Genzyme Tissue Repair
64 Sidney Street
Cambridge, MA 02139-4136 USA
Telephone: 800-453-6948 or 617-494-8484
Fax: 617-252-0877

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Cartilage Biopsy Transport Kit

For the further manufacturing of autologous cultured chondrocytes, Carticel™.

DIRECTIONS FOR USE

DESCRIPTION:

The Cartilage Biopsy Transport Kit consists of a plastic transport cylinder containing one 50 mL plastic screw-top tube with 40 mL biopsy transport medium and two Tyvek envelopes containing a Biopsy Transmittal Notice, Cartilage Biopsy Transport Kit Directions for Use, a Return Shipping Address Label (Federal Express), two "not tested for biohazards" labels (one label for the biopsy transport cylinder and one label for the shipping container), a service registry to be filled out by the clinician, patient consent form, and a service registry to be filled out by the patient. The cylinder also includes foam cushioning material, and one absorbent sheet. The biopsy transport medium is red sterile medium containing DMEM, Phenol Red and Gentamicin and has a pH of 7.0-7.4. The biopsy transport medium contains no preservatives and has the following composition:

Gm/L in 50 mL Centrifuge Tube:	
DMEM DPM (ChemStock 094-5900):	6.2
L-Cystine 2HCL:	0.063
L-Glutamine:	0.584
D-Glucose (Dextrose):	3.5
Hepes:	5.958
Phenol Red:	0.015
Gentamicin Sulfate:	50 mcg / mL
L-Tyrosine Disodium Salt:	0.104
Sodium Bicarbonate:	3.7
Sodium Chloride:	1.25

INTENDED USE:

The Cartilage Biopsy Transport Kit is intended for storage and transport of cartilage biopsy for the preparation of autologous cultured chondrocytes, Carticel™.

WARNING:

The Cartilage Biopsy Transport Medium is not intended for direct injection or intravenous administration.

Recommended storage:

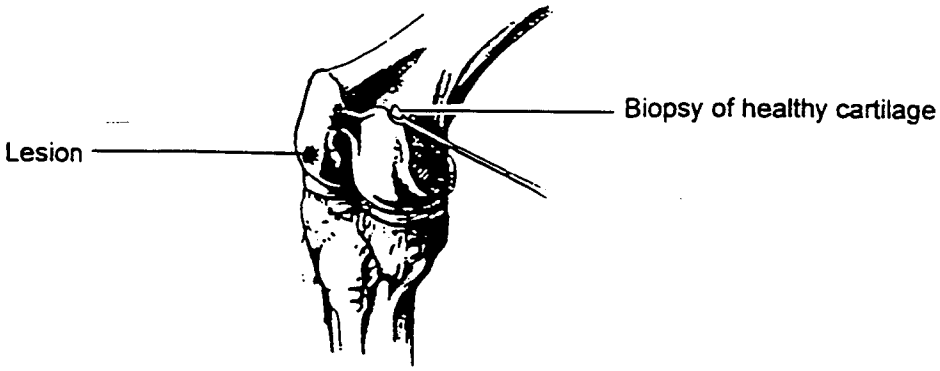
- Refrigerate Cartilage Biopsy Transport Kit Cylinder and refrigerant packs or entire box with contents at +2°C to +8°C (36°F to 46°F).
- **Do not freeze** Cartilage Biopsy Transport Kit Cylinder or refrigerant packs.
- Do not discard shipping container. Shipping container will be used to transport biopsy back to Genzyme Tissue Repair (GTR).

Biopsy Procurement:

Please see GTR Surgical Manual #65021 for detailed instructions on biopsy procurement.

BIOPSY PROCUREMENT ADVISORY:

1. The procedure is carried out through an arthroscope.
2. Using a ring curette or curved notchplasty gouge, **harvest 2 full-thickness slices.**

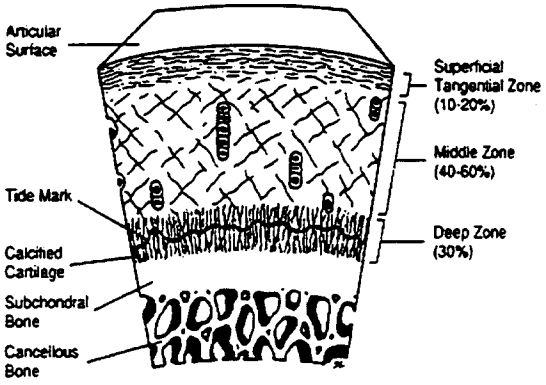


Obtain healthy cartilage slices measuring approximately 5 x 8 mm (total slices) from a lesser load-bearing area on the upper medial or lateral femoral condyle of the damaged knee. All bone inadvertently removed with cartilage will be discarded before processing.

3. Some punctate bleeding may occur, but is to be avoided if possible.

4. The final surface area of the cartilage removed should be approximately 40mm^2 (5 mm wide by 8 mm long).

5. The biopsy must be full-thickness and should include a small amount of bone which will be removed prior to processing the biopsy.



6. Using strict sterile technique, remove cartilage slices from the knee joint with forceps. Place biopsy into the unexpired biopsy transport medium tube provided in the cartilage biopsy transport kit.

7. For packaging, labeling, and shipping instructions, please refer to the Cartilage Biopsy Transport Kit Directions for Use included with the cartilage biopsy transport kit package.

Procedure:

Upon receipt of the Cartilage Biopsy Transport Kit

1. Remove the square foam insert from top of shipping container.

2. Remove the plastic biopsy transport cylinder from kit and twist off lid.

3. Remove biopsy transport medium tube from cylinder. (Caution: the **Exterior** of the tube is not sterile).

4. Check biopsy transport medium tube for expiration date, color, particulates, turbidity and leakage. Do not use if the tube is expired (expiration date is indicated on each tube) or if the tube has leaked. Do not use the tube if the color of the medium is yellow, or if obvious particulate matter, precipitate or turbidity is evident in the medium.

5. Replace the tube in the cylinder. Store the cylinder and the refrigerant packs at +2°C to +8°C (36°F to 46°F) until use. **Do not freeze** Biopsy Transport Kit Cylinder or refrigerant packs.

Day of Surgery:

1. Remove the plastic biopsy transport cylinder from the refrigerator and twist off lid.

2. Remove biopsy transport medium tube from cylinder. (Caution: the **Exterior** of the tube is not sterile).

3. Check biopsy transport medium tube for expiration date, color, particulates, turbidity and leakage. Do not use if the tube is expired (expiration date is indicated on each tube) or if the tube has leaked. Do not use the tube if the color of the medium is yellow, or if obvious particulate matter, precipitate or turbidity is evident in the medium.

4. Twist off tube cap.

5. Using sterile technique, place biopsy into transport medium tube.

6. Place the cap on the tube and twist to secure. Note that the cap has a two stage seal. ENSURE CAP IS SEALED TIGHTLY!

7. Enter the patient name and date of biopsy on the label on Cartilage Biopsy Transmittal Notice (Part No. 65007). The GTR Patient ID number is preprinted on that same label. Place the label on the biopsy transport medium tube. Physician's copy of Cartilage Biopsy Transmittal Notice with patient's name, date of biopsy, and preprinted GTR Patient ID number should be filed with patient's permanent records.

Packaging of biopsy

8. Insert biopsy transport medium tube containing cartilage sample back into the foam insert within the plastic cylinder, return the upper foam insert into the top of the cylinder, and place the lid on the cylinder and twist to secure. Place biohazard label (Part No. 64029) on the transport cylinder.

9. Insert cylinder into the shipping container.

10. Remove the two cold refrigerant gel packs from the refrigerator and place them on either side of the cylinder.

11. Place square foam insert on top of the cylinder.

12. Complete and enclose the Biopsy Transmittal Notice found in one of the Tyvek envelopes.

13. Secure the shipping container with tape.

14. Apply the biohazard label (Part No. 64028) on the shipping box.

15. Call GTR Customer and Patient Services at 800-453-6948 or 617-494-8484 (24 hours a day and seven days a week) to arrange biopsy pick-up.

HOW SUPPLIED:

The Cartilage Biopsy Transport Kit is supplied as a plastic transport cylinder containing one 50 mL plastic screw-top tube with 40 mL biopsy transport medium. The cylinder also contains foam cushioning material and one absorbent sheet. The kit includes two Tyvek envelopes packaged in the shipping container. One of the two Tyvek envelopes contains Biopsy Transmittal Notice, Cartilage Biopsy Transport Kit Directions for Use, a Return Shipping Address Label (Federal Express), and a service registry to be filled out by the clinician. The other envelope contains a patient consent form and a service registry to be filled out by the patient.

The Cartilage Biopsy Transport Kit and two Tyvek envelopes are packaged in an outer cardboard shipping container measuring 29.2 x 22.9 x 29.2 cm (11-1/2" x 9" x 11-1/2"), with plastic and foam insert. The cardboard box also includes two refrigerant packs and one foam insert.

The biopsy transport medium is red sterile medium containing DMEM, Phenol Red, and Gentamicin and has a pH of 7.0 - 7.4. The biopsy transport medium contains no preservatives.

Store the Cartilage Biopsy Transport Kit Cylinder and its content at +2°C to +8°C. Do not freeze the Cartilage Biopsy Transport Kit Cylinder or the refrigerant packs. Do not use if the tube is expired or if the tube has leaked. Do not use the tube if the medium is yellow or if obvious particulate matter, precipitate or turbidity is evident in the medium.

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

Manufactured by:
Genzyme Tissue Repair
64 Sidney Street, Cambridge, MA 02139